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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,230	08/12/1999	HARUKI OKMURA	OKAMURA=2E	2359

1444 7590 06/03/2005

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EXAMINER
JIANG, DONG

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/373,230	OKMURA ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9, 11, 14 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *7-9* is/are allowed.

6)☒ Claim(s) *1-6,11,14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 08 March 2005 is acknowledged and entered. Following the amendment, claims 1-3 and 11 are amended, and claims 15 and 17 are canceled.

Currently, claims 1-9, 11, 14 and 16 are pending and under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 15 and 17 are moot as the applicant has canceled the claims.

Rejections under 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-6 and 11 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record set forth in the previous Office Actions mailed on 05 January 2004, and 09 September 2004.

Applicants argument filed on 08 March 2005 has been fully considered, but is not deemed persuasive for reasons below.

At pages 10-11 of the response, the applicant argues that claim 3 has been amended to further define the variant by adding biological activity, purity and assay (parts (3), (5) and (6)), that the variants are now strictly defined, and the metes and bounds of claim 3 are clear even through the claim does not specify % sequence identity the variant and SEQ ID NO:2, and that a variant not having all (1) to (6) is not encompassed by claim 3 even though it may have very high sequence identity with SEQ ID NO:2. This argument is not persuasive because these features do not add much in terms to define the structure of the ambiguous "sequence variants" of SEQ ID NO:2. For example, distinct molecules of functional equivalent of SEQ ID NO:2 may have the same biological activity as that in part (3), especially in context with the recitation of "replacing at least one amino acid" in the claim. The purity recited in part (5) does not have

any thing to do with the structure of the molecule; and finally, the antibody binding assay in part (6) merely requires a common epitope, which is just a few amino acids, may not have any association with the functional activity, and may be shared by other molecules. As such, the metes and bounds of the claim still cannot be determined. A functional equivalent of SEQ ID NO:2 may have all (1) to (6), but it would not be a "sequence variant" of SEQ ID NO:2, and its sequence structure is still unclear.

Claim 11 remains indefinite for the reasons of record set forth in the last Office Action mailed on 09 September 2004. The claim is directed to an IGIF or IL-18, which possesses "a part ... of the amino acid sequence of SEQ ID NO:2" (part (4)), and "*reacts* with a mAb specific to ... or a sequence variant of the protein having one or more of the antigen fragments of the amino acid sequence of SEQ ID NO:2" (the last part of the claim), which reads on a functional equivalent with undefined structure. The newly added limitations in parts (3), (5) and (6), which are the same as that in claim 3, do not further define the structure of the molecule for the same reasons above. As such, the metes and bounds of the claim still cannot be determined.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-6 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a specific variant of said protein, which has an amino acid sequence of SEQ ID:2 where residue 70 is methionine or threonine, does not reasonably provide enablement for with claims to variants having physicochemical and functional properties listed in parts (1) to (4) of claim 3, and having the amino acid sequence of SEQ ID NO:2 with at least one amino acid residue in SEQ ID:2 replaced with different amino acid, or at least one amino acid residue deleted or added to the N-terminus of SEQ ID:2 while not substantially altering physicochemical properties of the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make the invention commensurate in scope with these claims, for the reasons set forth in the previous Office Actions.

Applicants argument filed on 08 March 2005 has been fully considered, but is not deemed persuasive for reasons below.

At page 12 of the response, the applicant repeatedly argues that a protein of claim 3 is well defined by the physicochemical properties (1) to (6) even through the claim does not specify % sequence identity the variant with respect to SEQ ID NO:2, that a skilled person would easily understand what protein would satisfy all of (1) to (6), and would easily obtain said protein. This argument is not persuasive because, as addressed above, the claim encompass functional equivalent of SEQ ID NO:2 without defined sequence structure. As such, a skilled person would not be able to make the variants in a manner commensurate in scope with the claim.

Claims 1, 2, 11, 14 and 16 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a protein with SEQ ID NO:2, wherein residue 70 is methionine or threonine, does not reasonably provide enablement for any IL-18 (claims 1, 2, 16 and 17, for example) or variants with properties listed in these claims (claims 11, 14 and 15, for example). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims, for the reasons set forth in the previous Office Actions.

Applicants argument filed on 08 March 2005 has been fully considered, but is not deemed persuasive for reasons below.

On pages 13-14 of the response, Applicants argue that one of skill in the art could easily have obtained a sequence variant of SEQ ID NO:2; that the newly added limitations of biological activity, purity and antibody assay in parts (3) to (5) in claims 1, 2, and 11 better define the protein; that the "antigenic fragment" recited in claim 11 is inherent of IL-18 of SEQ ID NO:2; and that it would be easy for a skilled person to obtain a protein defined in claim 11. This argument is not persuasive because the newly added limitations do not help to further define the protein for the same reasons above. Further, although the "antigenic fragment" recited in claim 11 may be inherent of IL-18 of SEQ ID NO:2, neither the claim nor the specification discloses or

define such a "antigenic fragment" specific for SEQ ID NO:2, and thus, the sequence structure of "antigenic fragment" is unknown. As such, one of skill in the art cannot make the invention commensurate in scope with the claims. Applicants further argue, at page 14 of the response, that claims 14 and 16 find support in the specification, which provides enablement for the claims. This argument is not persuasive because claims 14 and 16 are not amended.

Claims 1-6, 11, 14 and 16 remain further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the previous Office Actions.

Applicants argument filed on 08 March 2005 has been fully considered, but is not deemed persuasive for reasons below.

On page 15 of the response, Applicants argue that the sequence of the functional variants does not have to be explicitly given or the % sequence identity of a variant having a different length than SEQ ID NO:2, and that one can quite easily and unambiguously know by mere calculation and prediction how much deletion or addition of residues from termini would still retain the recited properties. This argument is not persuasive because it would be easily calculated and predicted if the claimed variants were made or the structure thereof were given, however, this is not the case here. The specification does not disclose any of such variants, nor provides structural and functional relationship of SEQ ID NO:2, so that a skilled in the art could follow as a guidance to make the claimed molecules. The issue is not how to calculate the % sequence identity of a variant in comparison to SEQ ID NO:2, rather, the issue is that a skilled in the art cannot envision the detailed chemical structure of the encompassed functional variants regardless of the complexity or simplicity of calculating the % sequence identity. The compound itself is required. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, 11, 14 and 16 remain rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura *et al.* (*Infect. Immun.* 61: 64-70, 1993), for the reasons set forth in the previous Office Actions, paper Nos. 4, 7 and 13, and the Office Action mailed on 09 September 2004.

Applicants argument filed on 08 March 2005 has been fully considered, but is not deemed persuasive for reasons below.

Applicants, once again, present the similar argument as that in the previous responses.

On page 16 of the response, applicants argue that the claimed protein is not one treated on SDS-PAGE but rather one obtained such as in Experiment 1 without treatment on SDS-PAGE, however, the claimed protein retained the same activity even after treatment on SDS-PAGE, and that, by contrast, Nakamura's factor losses its activity after SDS-PAGE. This argument is not persuasive because there is simply no support in the specification for such an assertion.

On page 17 of the response, applicants argue repeatedly that the claimed protein has a molecular weight of 19,000±5,000 (14-24 kDa) on both gel filtration and SDS-PAGE; that, by contrast, Nakamura's factor has a molecular weight of 70-75 kDa on gel filtration, and 50-55 kDa on SDS-PAGE; and that the claimed protein is not same as Nakamura's factor. This argument is not persuasive because as addressed extensively in the previous Office Actions (paper Nos. 7 and 13), a subsequent study published by Okamura et al. (the same group of investigators) demonstrates that the molecular mass of 75 kDa IGIF was reduced to 19 kDa on 0.1% SDS-PAGE in the presence of DTT, and the N-terminal amino acid sequence is the same as that of IGIF from the liver, "thus IGIF in the serum sample was proved to be the same IGIF as that found in the liver extract". The existence of merely different physical forms of the same molecule does not render the molecule itself patentably distinct in the absence of evidence to the contrary.

Applicants further argue repeatedly, on page 17 of the response, about the purity of the molecule as that the difference in purity sometimes renders a "chemical substance" patentably distinct from the prior art; that, for example, when the claimed protein is used for medical purposes, higher purity is desirable, and that it would be very difficult to obtain a specific antibody to, or to determine the amino acid sequence of the claimed protein without the claimed protein being isolated to high purity. This argument is not persuasive because Okamura also purified his factor to a single band on SDS-PAGE (page 66, the last paragraph of the right column).

Conclusion:

Claims 7-9 are allowable.

Claims 1-6, 11, 14 and 16 are rejected.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Lorraine Spector
LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
5/18/05